REMARKS

Applicant wishes to thank the Examiner for the careful consideration given to the present application; and would like to thank the Examiner's supervisor, Sreeni Padmanabhan, for kindly conducting the interview on September 2, 2009 in Examiner Carter's absence. The interview was informative regarding the Office's view of the Yu '259 reference and each of the Yu, et al. references being submitted with the Supplemental IDS. As discussed during the interview, Applicant thought it would be helpful that the Office have a better understanding of the distinctions between erythema of rosacea and the general term "erythema" and has provided a general discussion regarding this topic in the Supplemental IDS section of this response.

By entry of this paper, claims 1 and 3-6 and 13-16 are pending, claims 4-6 are withdrawn in light of the species election and claims 2, 7-12 and 17-24 are canceled. Claim 1 has been amended to recite a particular amount of the alpha-1 adrenoreceptor agonist. Claims 3-6 have been amended to correct an unintentional change in the claim language that occurred in the previous Amendment and Response. Additionally, new claims 25-63 are presented to focus the Examiner's attention on specific embodiments of Applicant's invention. Support for such amendments and claims can be found in, for example, paragraphs [0053], [0056] and [0083] of the specification. For clarity, the claims currently being presented can be grouped in broad categories of *treating erythematous rosacea* with:

- a composition comprising about 0.05% to about 30% of an alpha-1 adrenoreceptor agonist (claim 1);
- a composition comprising about 0.05% to about 30% of oxymetazoline (claim 26);
- a composition consisting essentially of about 0.05% to about 30% of an alpha-1 adrenoreceptor agonist (claim 35); and
- a composition comprising an alpha-1 adrenoreceptor agonist as the sole active agent (claim 48).

Applicant has amended the claims to clarify that the erythema to be treated is erythema resulting from rosacea. As was discussed during the interview, the general term "erythema" can not be equated with erythema of rosacea. Thus, the claims currently focus on the

treatment of erythema resulting from rosacea, not erythema generally or erythema resulting from any other condition. Applicant expressly reserves the right to pursue claims to erythema generally, but the present claims focus on erythema resulting from rosacea solely to facilitate allowance of the present application. As will be appreciated by those of skill in the art, erythema resulting from rosacea is quite different from other erythemas. Each of the claims presented herein are believed to be allowable over the cited art. Applicant's position is reinforced by the remarks presented below. Each of the rejections set forth in the Office Action are addressed below in the order presented therein.

35 U.S.C. § 103

The Examiner has rejected claims 1-3 and 13-16 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yu '259 in view of Applicant's statements in the specification (referenced as specification, page 1, background of the invention, paragraphs 1 and 2; page 7, lines 16-17 of Applicant's Response). Applicant respectfully disagrees, particularly in light of the amendments presented herein. As will be described in greater detail below: Yu '259 can not be properly combined with Applicant's statements to otherwise allegedly establish a *prima facie* case of obviousness; and even if the art is combinable, Yu '259 in combination with Applicant's statements do not satisfy a *prima facie* case of obviousness, as there is nothing in the cited art that suggests that an alpha-1 adrenoreceptor agonist would be effective to treat erythema, let alone erythema resulting from rosacea, including in particular the recited amounts. Further, any *prima facie* case of obviousness purportedly established by the Office is rebutted by the lack of a reasonable expectation of success. Finally, any *prima facie* case of obviousness purportedly established by the Office is also rebutted by the long-felt, but unsatisfied need to treat erythema resulting from rosacea. In light of the amendments to the claims and the remarks presented herein, the present claims should be passed to issue.

The cited art is not properly combinable, as one ordinarily skilled in the art would not consider erythema of rosacea a vasodilatory disease that could be treated with a vasoconstrictor. The Office has taken the position that the combination of select statements by the Applicant that rosacea is associated with dilation of the facial blood vessels and

oxymetazoline is a vasoconstrictor, one skilled in the art would have found it obvious and motivated to combine Yu '259's method of topically administering oxymetazoline; however, this combination is not proper and can not be used to establish a *prima facie* case of obviousness.

As acknowledged by Applicant in the specification and as understood by one skilled in the art, the pathophysiology of rosacea and erythema of rosacea is relatively unknown (which in turn, have made effective treatments largely unattainable to date). *See* specification at paragraph [0010]; *see also* Bamford et al., "*Rosacea: Current Thoughts on Origin*," 20(3) SEMINARS IN CUTANEOUS MED. AND SURG., 199-206 (2001) (attached hereto as **Exhibit A**); Crawford et al., "*Rosacea: I. Etiology, pathogenesis and subtype classification*" 51(3) J. AM. ACAD. DERMATOL. 327-41 (2004) (attached hereto as **Exhibit B**).

While the Office's rationale appears seemingly logical and simple, it is not. The Office's logic is that oxymetazoline is a vasoconstrictor and rosacea involves dilated blood vessels, and therefore it would be obvious to treat erythema of rosacea with oxymetazoline. However, this "connection" is not so simple, and the Office's logic is flawed. In fact, as demonstrated in Cunliffe et al., an α_2 adrenoreceptor agonist clonidine, which is a known vasoconstrictor, had *no effect* on rosacea or the flushing associated with rosacea (*see* Cunliffe et al., "*Clonidine and facial flushing in rosacea*" 1 (6053) BR. MED. J. 105 (1977) attached hereto as **Exhibit C**). In addition, topical corticosteroids, which are known to have potent topical vasoconstrictive activity, are *contraindicated* in patients with rosacea because the cutaneous vessels rapidly develop tolerance to the vasoconstrictive action of the steroids (tachyphylaxis), which results in the need for more frequent, higher doses in order to maintain any vasoconstrictive effect, and ultimately results in persistently dilated unresponsive vessels and an *increase* in erythema, telangiectasias and/or inflammatory lesions ("steroid rosacea"). The fact that (i) the art is devoid of any teaching that demonstrates the effective use of alpha-1 adrenoreceptor agonists to treat erythema, (ii) multiple known vasoconstrictors have been previously tried and are either ineffective or exacerbate the erythema, and (iii) erythematous rosacea does not otherwise have an established effective therapy, is demonstrative of the inventive aspects of the present application. In fact, the link put forth by the Office to establish its obviousness rejection is flawed.

As the vessels appear to be *abnormally* responsive to local (i.e., neural) and systemic vascular stimuli in erythema resulting from rosacea, there is no reason to believe and certainly no reason to presume that they would respond in a normal way (with vasoconstriction) to exogenously administered (e.g., topically applied) alpha adrenergic stimuli. In fact, the very fact that the vessels appear to be abnormally insensitive to endogenous vasoconstrictive stimulation (or abnormally sensitive to endogenous vasodilatory stimulation) would lead one to believe that such an approach would be ineffective and may be the reason(s) that treatment of the erythema of rosacea has not been approached this way in the past. Accordingly, the presence of dilated blood vessels in rosacea would not lead one ordinarily skilled in the art to try a vasoconstrictor, even absent the past failures with other vasoconstrictors. Additionally, there are numerous other current peer-reviewed theories of the pathophysiology of rosacea that do not involve mere vasodilation, but rather involve an abnormal central nervous system mediated response to heat, an increased amount of inflammatory mediators (substance P, vasoactive intestinal peptide, etc.), climatic exposures resulting in dermal blood vessel and dermal connective tissue damage, primary dermal matrix degeneration, the use of certain drugs, chemicals and ingested agents, pilosebaceous unit abnormalities and microbial organisms (*D. folliculorum, H. pylori*). *See* Crawford, et al., *supra* (attached hereto as **Exhibit B**). Each of the foregoing alternative theories eviscerates the purported simple causative link between dilated blood vessels and rosacea.

The cited art does not teach any effective amounts of an alpha-1 adrenoreceptor agonist for treating erythema of rosacea. First and foremost, as amended, the current claims require the topical administration of a composition comprising an effective amount of an alpha-1 adrenoreceptor agonist, and in particular many of the claims recite that the effective amount is about 0.05% to about 30% of at least one alpha-1 adrenoreceptor agonist and a carrier, wherein the alpha-1 adrenoreceptor agonist treats the erythema resulting from rosacea. It is respectfully submitted that neither Yu '259 nor Applicant's own statements alone or in combination teach, suggest or otherwise render obvious an about 0.05% to about 30% alpha-1 adrenoreceptor agonist composition, wherein such an amount of the alpha-1 adrenoreceptor agonist treats erythema resulting from rosacea. Yu '259 is completely silent as to any amount of

oxymetazoline to be administered to a subject, and (as discussed in greater detail below), the amount of oxymetazoline to be administered based upon the teachings of Yu '259 would only be understood by one skilled in the art to be an amount that would be administered in combination with the active agent of Yu '259, namely a polyhydroxylactone. In order to identify the amount of an alpha-1 adrenoreceptor agonist that would be effective in treating erythema resulting from rosacea would require one ordinarily skilled in the art to understand that an alpha-1 adrenoreceptor agonist alone would or could be effective to treat erythema associated with rosacea. Without this underlying understanding (which is not provided by Yu '259 in combination with Applicant's statements), one skilled in the art would not be motivated to identify a particular amount that would be effective.

Yu '259 does not teach that oxymetazoline or any other α_1 adrenoreceptor agonist would be useful for treating erythema or rosacea. At best, Yu '259 teaches that oxymetazoline could be *added* to or included in a composition that contains a first agent (i.e., a polyhydroxylactone) that is otherwise useful for treating rosacea. There is simply no teaching or suggestion in Yu '259 that oxymetazoline itself (or any of the other agents in Yu '259's list) could be useful to treat erythema resulting from rosacea.

Yu '259 teaches that a first agent (*e.g.,* polyhydroxylactone) can be used to treat skin conditions, including rosacea. Yu '259 further discloses that additional agents may be used for other purposes. Oxymetazoline appears in Yu '259 only as part of a 42-line list of "[a]dditional exemplary agents." The exemplary agents are ***additional*** "agents added to enhance the cosmetic, pharmaceutical, or other properties of the compositions." Paragraph [0045] sets out potential purposes for the additional agents which includes a wide range of indications (that do not include treatment of rosacea or erythema). Notably, there is nothing in this list that teaches or suggests any additional agents would be useful in treating rosacea or erythema resulting from rosacea, as presently claimed. Yu '259 relies on the first active (*e.g.,* a polyhydroxylactone) compound to treat several skin conditions of which rosacea and erythema are *separately* included. The additional agent, such as oxymetazoline, is present for other purposes, such as those listed in paragraph [0045] and for which the agent was already known to be useful. It is notable that paragraph [0045] does not disclose "antirosacea agents," despite

disclosing *e.g.*, antiacne agents, antipsoriatic agents, and antidermatitis agents, clearly indicating that there was neither the intention to include rosacea as a disease state that could be treated, nor any expectation that the cited agents would treat it. Clearly, none of the agents listed, including oxymetazoline, are listed for the purpose of treating rosacea or erythema. Certainly, none are listed as specifically treating erythema resulting from rosacea.

The disclosure of a long list of compounds with no clear use and no guidance from the art does not make obvious the present claims. The disclosure of a long list of compounds does not necessarily render a claim to the use of one such compound obvious, particularly if the reference indicates a preference that leads away from the claimed compound. *In re Baird*, 16 F.3d. 380 (Fed. Cir. 1994). In the instant case, Yu '259's laundry list of added agents, which includes oxymetazoline, does not render the instantly claimed methods obvious, particularly because oxymetazoline (and the other additional agents) are listed for purposes other than treating the disorders treated by the first agent (*e.g.* polyhydroxylactone). One skilled in the art would understand that many of the agents listed in Yu '259 would exacerbate or otherwise be contraindicated in rosacea, such as: corticosteroids (see *infra*), capsaicin (the active component of chili peppers and pepper spray that produces a sensation of burning in any tissue it contacts), 5-fluorouracil (a topical chemotherapy agent that produces a marked inflammatory response and "persisting erythema" in patients with rosacea, *see* Sams, *"Untoward response with topical fluorouracil,"* 97(1) ARCH. DERMATOL. 14-22 (1968) (attached hereto as **Exhibit D**)), podophyllin (a treatment of warts that is a caustic extract from the roots of *Podophyllum* species of plants that is very irritating to mucous membranes and skin) and others. Yu '259 fails to disclose or suggest a therapeutically effective amount of an alpha-1 adrenoreceptor agonist, and without a teaching or suggestion that oxymetazoline or any alpha-1 adrenoreceptor agonist could be useful for treating rosacea, one skilled in the art would not have been motivated to identify a therapeutically effective amount of such a compound and certainly would not have identified the range now recited in the amended and new claims.

The Office has not presented sufficient evidence as to why the use of oxymetazoline for the treatment of erythema of rosacea would have been obvious. Ultimately, the Office appears to be alleging that it would have been "obvious to try" oxymetazoline in the

claimed methods because it is a vasoconstrictor and rosacea involves dilated blood vessels. Obvious to try, however, is not analyzed in a vacuum. As the Supreme Court recently stated:

> When there is a design need or market pressure to solve a problem and there are a ***finite number*** of identified, ***predictable*** solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the ***anticipated success***, it is likely the product not of innovation but of ordinary skill and common sense.

KSR v. Teleflex, 82 USPQ2d 1385, 1390 (2007) (emphasis added). Here, the Office has failed to show that there were a "finite number of identified, predictable solutions" that would have led one of skill in the art to anticipate success using oxymetazoline to treat erythema associated with rosacea. Certainly, there was no anticipated success given the failure of other drugs, including an alpha-2 adrenoreceptor agonist, for treating rosacea. A similar attempt to invalidate a patent using "obvious to try" was also rejected by the Federal Circuit in *Takeda Chemical Indus. Ltd. v. Alphapharm Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007).

In *Takeda*, the defendant argued that the claimed compound was obvious because it would have been "obvious to try" to make and use the compound. *Id.* at 1176. The court held that the invention was not obvious under the obvious to try standard because "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Id.* Here, like in *Takeda*, the prior art had not identified a predictable solution for a composition that would be effective in the claimed methods. Yu '259 merely discloses a list of additional agents that may be used in combination with polyhydroxylactones, but does not disclose that oxymetazoline or any of the other additional agents should be selected as a compound for further investigation as a treatment for erythema associated with rosacea. Furthermore, given the unpredictability of the pharmaceutical arts, one of skill in the art could not predict what compounds would and would not work to treat erythema resulting from rosacea since Yu '259 provides no guidance whatsoever for selecting a potential agent. Additionally, by the notable omission of anti-rosacea agents from the laundry list of agents that could be included in the formulation, it is clear that Yu '259 never even contemplated the possibility that their

compound might be useful for the treatment of the erythema of rosacea, nor asserted that the inclusion of oxymetazoline in such a composition would be for the purpose of treating erythema of rosacea.

No reasonable expectation of success of treating erythema of rosacea with an alpha-1 adrenoreceptor agonist because of previous failures and lack of guidance for success. Applicant respectfully submits that there is no reasonable expectation of success, thereby rebutting any purported *prima facie* case of obviousness. As demonstrated in Cunliffe et al. *supra*, the vasoconstrictor clonidine was ineffective in treating erythema resulting from rosacea, evidencing the complete lack of predictability in this field, and in particular with respect to alpha adrenoreceptor agonists and erythema resulting from rosacea. Therefore, there would not have been a reasonable expectation of success that an alpha-1 adrenoreceptor agonist would be effective to treat erythema resulting from rosacea. As consistently proffered by the Office, the pharmaceutical arts and therapeutic methods are inherently unpredictable given the complexity of the disease and the interplay between administration of a therapeutic agent and the human body. In addition, as noted *supra*, the pathophysiology of rosacea has been poorly understood to date. Further, the art, including Yu '259, fails to provide any guidance of what parameters are critical or what may be successful in treating erythema of rosacea.

As recently instructed by the Federal Circuit, where there are numerous possible choices "where the prior art [gives] either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful" the "courts should not succumb to hindsight claims of obviousness." *The Proctor & Gamble Co., v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996-97 (Fed. Cir. May 13, 2009). The court explained that "patents are not barred just because it was obvious 'to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'" *Id.*

In the present case, not only is there evidence that the topical administration of a "vasoconstrictor" (i.e., clonidine) was ineffective in treating erythema of rosacea, the art is inherently unpredictable and provides little to no guidance on the characteristics or activities

necessary or desirable for identifying an effective treatment. For a claim to be obvious one of skill in the art must have had a reasonable expectation of success. Thus, because the Office has failed to demonstrate that one of skill in the art would have had a reasonable expectation of success, the claims are not obvious.

Long-felt, but unsatisfied need for a treatment of erythema of rosacea. Erythema resulting from rosacea has been a persistent problem faced by the dermatological community and its patients since the disease was first described. Any purported *prima facie* case of obviousness is further rebutted by the fact that there is a long-felt, yet unsatisfied need for an effective treatment of rosacea. As set forth in Applicant's specification at paragraph [0007]:

> there is currently no consistently effective treatment of any kind for the acute flushing and blushing of rosacea. John E. Wolf, Jr, MD, professor and chairman of the Department of Dermatology, Baylor College of Medicine, Houston, Tex., addressed this very issue in the meeting highlights for the Fall Clinical Dermatology Conference in Las Vegas, Nev., 2002. According to Dr. Wolf, "By far the most difficult-to-treat and challenging patients with rosacea are the patients who flush and blush. Indeed, no therapy works consistently in these patients." Dr. Wolf further asserted, "In my opinion, lasers are the most effective treatment for erythemato-telangiectatic rosacea, but I think they are much less effective for flushing and blushing patients. Some patients will respond but most do not."

In fact, in a recent survey published in 2007, dermatologists rated the treatment/reduction of erythema in rosacea as the highest unmet medical need in rosacea (by 60% of the dermatologists), with the next unmet medical need in rosacea being rated by only 18% of the surveyed dermatologists (Collagenex Corporation/IMS Demand Study as presented at The Fourth Annual Healthcare Conference, November 27-28, 2007, New York, New York attached hereto as **Exhibit E**).

The poor understanding of the pathophysiology of the disease has resulted in a dearth of focused, useful clinical studies to even guide the development of new therapies. As set forth in a recent Cochrane review of rosacea therapies to assess the efficacy and safety of such rosacea therapies, the authors state that there are "significant limitations in the quality of

evidence available for most treatments" and suggests that available data fails to provide a clear treatment for rosacea. *See* van Zuuren, et al., "*Systematic review of Rosacea Treatments,*" 56(1) J. AM. ACAD. DERMATOL. 107-115 (2007) (attached hereto as **Exhibit F**). As noted in 2005 in a New England Journal of Medicine Clinical Practice review of rosacea:

> [t]he causes and pathogenesis of rosacea remain poorly understood. Data from randomized, clinical trials on the efficacy and optimal duration of many of the therapies, including complementary therapies that are frequently used by patients, are lacking. The possibility of emergence and carriage on the skin of resistant organisms is a concern with regard to the prolonged use of topical and systemic antibiotics....There are no specific guidelines for the management of rosacea.

Powell, "*Clinical Practice: Rosacea,*" 352(8) N. ENGL. J. MED. 793-803 (2005) (footnotes omitted) attached hereto as **Exhibit G**. Ultimately, it is respectfully submitted that the fact that Applicant has identified an effective treatment for erythema of rosacea, which has heretofore been largely unmet by the currently available therapies sufficiently rebuts any purported *prima facie* case of obviousness.

In light of the remarks and amendments presented herein, it is believed that pending claims 1, 3, 13-16 and new claims 25-63 are in condition for final allowance and notice to such effect is respectfully requested. Additionally, Applicant respectfully requests rejoinder of claims 4-6.

NEW CLAIMS

It is also respectfully submitted that new claims 35-47 recite that the subject is administered a composition that ***consists essentially of*** an alpha-1 adrenoreceptor agonist. It is respectfully submitted that such claims are also not anticipated or rendered obvious by Yu '259 as the use of "consisting essentially of" in such claims specifically excludes the presence of an additional active ingredient that would treat rosacea. Additionally, Applicant respectfully requests rejoinder of claims 37-39 that are withdrawn in light of the species election.

New claims 48-63 claim methods treating rosacea by administering compositions where the alpha-1 adrenoreceptor agonist is **"the *sole* active agent."** Support for such new claims can be found throughout Applicant's specification, but particularly at paragraph [0053] which clearly indicates ". . . when included in the typical embodiment as the sole active ingredient . . ." Yu '259, to the extent it allegedly teaches the use of oxymetazoline, requires at least two active agents, the polyhydroxylactone and the added agent. Additionally, Applicant respectfully requests rejoinder of claims 50-52 that are withdrawn in light of the species election.

Although Applicant maintains the position that Yu '259 does not disclose oxymetazoline for treatment of rosacea or erythema resulting from rosacea, to the extent the Office maintains its rejection, at a minimum, the rejection should not apply to claims 35-63 that allow for only one active agent, the alpha-1 adrenoreceptor agonist.

Supplemental IDS

Applicant submits herewith a Supplemental Information Disclosure Statement ("IDS") citing additional references, including references that were cited in Applicant's recently filed and co-pending application directed to the treatment of purpura (U.S. Application No. 12/272,253), as well as references that appear to be related in subject matter to Yu '259. The references that appear related to Yu '259 include (i) U.S. Patent No. 6,335,023 to Yu et al. and (ii) U.S. Patent No. 6,824,786 to Yu et al. It is respectfully submitted that the subject matter of these newly cited Yu references as well as the other cited references are not relevant, and importantly fail to anticipate or render obvious the present claims as the references simply disclose potential treatments of skin erythema, and not a treatment for rosacea. Nothing in this submission should be construed as an admission of prior art, and Applicant reserves the right to contest the same.

While rosacea remains a disorder of uncertain etiology and pathogenesis, the abnormal flushing and persistent erythema appear to arise from a dysregulation in the cutaneous vasomotor response. Whether triggered by neurogenic, hormonal, thermal, topical or other stimuli, the dysregulation in the cutaneous vasomotor response ultimately results in abnormal and persistent dilation of facial blood vessels. The erythema of rosacea is not an inflammatory

reaction, though in some forms of the disease it may be accompanied by inflammatory lesions. The facial blood vessels are abnormally responsive to normal physiologic and external stimuli, whether because of abnormalities in alpha receptor density, an abnormal expression, function, distribution, or responsiveness of alpha-adrenergic receptors, or another as yet determined mechanism, and remain persistently dilated.

Moreover, erythema of rosacea is understood by one skilled in the art to be a distinct condition- one that is not response to topical treatments that are otherwise effective to treat erythema resulting from other causes or conditions. With reference to Applicant's specification, it should be noted that although the erythema of rosacea results from dilated blood vessels, rosacea is unlike other conditions displaying clinically similar redness (erythema). For example, erythemas caused by allergic and contact dermatitis, eczema, erysipelas, acne, and seborrheic dermatitis each respond to treatment of the underlying pathophysiologic state. The erythema of rosacea does not respond to the treatments employed for the other conditions. As the pathophysiology of the erythema of rosacea has yet to be elucidated, in fact, no satisfactory treatment for it exists. Thus, there continues to be a great need for a treatment of the specific erythema resulting from rosacea in light of its resistance to other known therapies that are effective in other conditions.

CONCLUSION

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,

By: .....
Raymond A. Miller
Reg. No. 42,891

Dated: September 17, 2009
PEPPER HAMILTON LLP
500 Grant Street
One Mellon Bank Center, 50th Floor
Pittsburgh, PA 15219
(412) 454-5813
(412) 281-0717 - facsimile